

What is claimed is:

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1. A method for improving production of a secondary metabolite by a fungus by increasing the yield of the secondary metabolite in the fungus, the method comprising modulating the expression of a gene involved in regulation of secondary metabolite production in a manner that improves the yield of the secondary metabolite, provided however, that when the secondary metabolite is isopenicillin N, then the modulation is not mediated by transcription factor CPCR1; when the secondary metabolite is sterigmatocystin, then the modulation is not through AflR, FadA, or FluG; when the secondary metabolite is aflatoxin, then the modulation is not through AflR; when the secondary metabolite is penicillin and the fungus is *Aspergillus nidulans*, then the modulation is not through mutations that result in expression of truncated forms of PacC or constitutively active forms of FadA; and when the gene involved in regulation of secondary metabolite production is from *Saccharomyces cerevisiae*, then the modulation is not through decreased activity or expression of Hog1, Bem2, Rim15, Sfl1, Ira1, Ssd1, Srb11, Swi4, Tpk3 or though increased activity or expression of Afl1, Dhh1, Inv7, Inv8, Ste21, Pet9, Mep2, Inv1, Inv5, Inv6, Inv9, Inv10, Inv11, Inv12, Inv13, Inv14, Inv15, Cdc25, Mcm1, Mga1, Phd2, Pho23, Ptc1, Rim1, Stp22, Tpk2 or Ypr1.

2. The method according to claim 1, wherein the modulation is overexpression of the gene.

3. The method according to claim 1, wherein the modulation is conditional expression of the gene.

4. The method according to claim 1, wherein the modulation is expression of a dominant mutation of the gene.

5. The method according to claim 4, wherein the dominant mutation is a dominant negative mutation.

6. The method according to claim 4, wherein the dominant mutation is a dominant positive mutation.

7. The method according to claim 4, wherein the dominant mutation is a dominant neomorphic mutation.

8. The method according to claim 1, wherein the modulation is mediated by a peptide modulator of gene expression.

9. The method according to claim 8, wherein the peptide modulator is an activator of gene expression.

10. The method according to claim 8, wherein the peptide modulator is an inhibitor of gene expression.

11. The method according to claim 1, wherein the modulation is mediated by a small molecule modulator of gene expression.

12. The method according to claim 11, wherein the small molecule modulator is an activator of gene expression. (D)

13. The method according to claim 11, wherein the small molecule modulator is an inhibitor of gene expression.

14. The method according to any of claims 1-13, further comprising the step of purifying the secondary metabolite from a culture of the fungus.

15. A method for improving production of a secondary metabolite by a fungus by increasing productivity of the secondary metabolite in the fungus, the method comprising modulating the expression of a gene involved in regulation of secondary metabolite production in a manner that improves the productivity of the secondary metabolite, provided however, that when the secondary metabolite is isopenicillin N, then the modulation is not mediated by transcription

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factor CPCR1; when the secondary metabolite is sterigmatocystin, then the modulation is not through AflR, FadA, or FluG; when the secondary metabolite is aflatoxin, then the modulation is not through AflR; when the secondary metabolite is penicillin and the fungus is *Aspergillus nidulans*, then the modulation is not through mutations that result in expression of truncated forms of PacC or constitutively active forms of FadA; and when the gene involved in regulation of secondary metabolite production is from *Saccharomyces cerevisiae*, then the modulation is not through decreased activity or expression of Hog1, Bem2, Rim15, Sfl1, Ira1, Ssd1, Srb11, Swi4, Tpk3 or though increased activity or expression of Afl1, Dhh1, Inv7, Inv8, Ste21, Pet9, Mep2, Inv1, Inv5, Inv6, Inv9, Inv10, Inv11, Inv12, Inv13, Inv14, Inv15, Cdc25, Mcm1, Mga1, Phd2, Pho23, Ptc1, Rim1, Stp22, Tpk2 or Ypr1.

16. The method according to claim 15, wherein the modulation is overexpression of the gene.
17. The method according to claim 18, wherein the modulation is conditional expression of the gene.
18. The method according to claim 15, wherein the modulation is expression of a dominant mutation of the gene.
19. The method according to claim 18, wherein the dominant mutation is a dominant negative mutation.
20. The method according to claim 18, wherein the dominant mutation is a dominant neomorphic mutation.
21. The method according to claim 18, wherein the dominant mutation is a dominant positive mutation.
22. The method according to claim 15, wherein the modulation is mediated by a peptide modulator of gene expression.

23. The method according to claim 22, wherein the peptide modulator is an activator of gene expression.

24. The method according to claim 22, wherein the peptide modulator is an inhibitor of gene expression.

25. The method according to claim 15, wherein the modulation is mediated by a small molecule modulator of gene expression.

26. The method according to claim 25, wherein the small molecule modulator is an activator of gene expression.

27. The method according to claim 25, wherein the small molecule modulator is an inhibitor of gene expression.

28. The method according to any of claims 15-27, further comprising the step of purifying the secondary metabolite from a culture of the fungus.

29. A method for improving production of a secondary metabolite in a fungus by increasing efflux or excretion of the secondary metabolite, the method comprising modulating the expression of a gene involved in regulation of secondary metabolite production in a manner that increases efflux or excretion the secondary metabolite.

30. The method according to claim 29, wherein the modulation is overexpression of the gene.

31. The method according to claim 29, wherein the modulation is conditional expression of the gene.

32. The method according to claim 32, wherein the modulation is expression of a dominant mutation of the gene.

33. The method according to claim 32, wherein the dominant mutation is a dominant negative mutation.

34. The method according to claim 32, wherein the dominant mutation is a dominant neomorphic mutation.

35. The method according to claim 32, wherein the dominant mutation is a dominant positive mutation.

36. The method according to claim 29, wherein the modulation is mediated by a peptide modulator of gene expression.

37. The method according to claim 36, wherein the peptide modulator is an activator of gene expression.

38. The method according to claim 36, wherein the peptide modulator is an inhibitor of gene expression.

39. The method according to claim 29, wherein the modulation is mediated by a small molecule modulator of gene expression.

40. The method according to claim 39, wherein the small molecule modulator is an activator of gene expression.

41. The method according to claim 39, wherein the small molecule modulator is an inhibitor of gene expression.

42. The method according to any of claims 29-41, further comprising the step of purifying the secondary metabolite from a culture of the fungus.

43. A method for improving production of a secondary metabolite in a fungus by decreasing production of side products or competing secondary metabolites, the method comprising modulating the expression of a gene involved in regulation of secondary metabolite production in a manner that decreases production of side products or competing secondary metabolites.

44. The method according to claim 43, wherein the modulation is overexpression of the gene.

45. The method according to claim 43, wherein the modulation is conditional expression of the gene.

46. The method according to claim 43, wherein the modulation is expression of a dominant mutation of the gene.

47. The method according to claim 46, wherein the dominant mutation is a dominant negative mutation.

48. The method according to claim 46, wherein the dominant mutation is a dominant neomorphic mutation.

49. The method according to claim 46, wherein the dominant mutation is a dominant positive mutation.

50. The method according to claim 43, wherein the modulation is mediated by a peptide modulator of gene expression.

51. The method according to claim 50, wherein the peptide modulator is an activator of gene expression.

52. The method according to claim 50, wherein the peptide modulator is an inhibitor of gene expression.

53. The method according to claim 43, wherein the modulation is mediated by a small molecule modulator of gene expression.

54. The method according to claim 53, wherein the small molecule modulator is an activator of gene expression.

55. The method according to claim 53, wherein the small molecule modulator is an inhibitor of gene expression.

56. The method according to any of claims 43-55, further comprising the step of purifying the secondary metabolite from a culture of the fungus.

57. A method for improving production of a secondary metabolite in a fungus by altering the characteristics of the fungus in a manner that is beneficial to the production of the secondary metabolite, the method comprising modulating the expression of a gene involved in regulation of secondary metabolite production in a manner that alters the characteristics of the fungus.

58. The method according to claim 57, wherein the altered characteristic is transition from hyphal growth to yeast form.

59. The method according to claim 57, wherein the altered characteristic is an increase or decrease in flocculence.

60. The method according to claim 57, wherein the altered characteristic is increased or decreased adhesion to a surface.

61. The method according to any of claims 57-60, wherein the modulation is overexpression of the gene.

62. The method according to any of claims 57-60, wherein the modulation is conditional expression of the gene.

63. The method according to any of claims 57-60, wherein the modulation is expression of a dominant mutation of the gene.

64. The method according to claim 63, wherein the dominant mutation is a dominant negative mutation.

65. The method according to claim 63, wherein the dominant mutation is a dominant positive mutation.

66. The method according to claim 63, wherein the dominant mutation is a dominant neomorphic mutation.

67. The method according to any of claims 57-60, wherein the modulation is mediated by a peptide modulator of gene expression.

68. The method according to claim 67, wherein the peptide modulator is an activator of gene expression.

69. The method according to claim 68, wherein the peptide modulator is an inhibitor of gene expression.

70. The method according to any of claims 57-60, wherein the modulation is mediated by a small molecule modulator of gene expression.

71. The method according to claim 70, wherein the small molecule modulator is an activator of gene expression.

72. The method according to claim 70, wherein the small molecule modulator is an inhibitor of gene expression.

73. The method according to any of claims 57-72, further comprising the step of purifying the secondary metabolite from a culture of the fungus.

74. A method for improving production of a secondary metabolite in a fungus by causing conditional lysis of the fungus, the method comprising modulating the expression of a gene involved in regulation of secondary metabolite production in a manner that causes conditional lysis.

75. The method according to claim 74, wherein the modulation is overexpression of the gene.

76. The method according to claim 74, wherein the modulation is conditional expression of the gene.

77. The method according to claim 74, wherein the modulation is expression of a dominant mutation of the gene.

78. The method according to claim 77, wherein the dominant mutation is a dominant negative mutation.

79. The method according to claim 77, wherein the dominant mutation is a dominant positive mutation.

80. The method according to claim 77, wherein the dominant mutation is a dominant neomorphic mutation.

81. The method according to claim 74, wherein the modulation is mediated by a peptide modulator of gene expression.

82. The method according to claim 81, wherein the peptide modulator is an activator of gene expression.

83. The method according to claim 81, wherein the peptide modulator is an inhibitor of gene expression.

84. The method according to claim 74, wherein the modulation is mediated by a small molecule modulator of gene expression.

85. The method according to claim 84, wherein the small molecule modulator is an activator of gene expression.

86. The method according to claim 84, wherein the small molecule modulator is an inhibitor of gene expression.

87. The method according to any of claims 74-86, further comprising the step of purifying the secondary metabolite from a culture of the fungus.

88. A method for improving production of a secondary metabolite in a fungus by increasing the resistance of the fungus to the deleterious effects of exposure to a secondary metabolite, the method comprising modulating the expression of a gene involved in regulation of secondary metabolite production in a manner that increases resistance to the deleterious effects of exposure to a secondary metabolite.

89. The method according to claim 88, wherein the modulation is overexpression of the gene.

90. The method according to claim 88, wherein the modulation is conditional expression of the gene.

91. The method according to claim 88, wherein the modulation is expression of a dominant mutation of the gene.

92. The method according to claim 91, wherein the dominant mutation is a dominant negative mutation.

93. The method according to claim 91, wherein the dominant mutation is a dominant positive mutation.

94. The method according to claim 91, wherein the dominant mutation is a dominant neomorphic mutation.

95. The method according to claim 88, wherein the modulation is mediated by a peptide modulator of gene expression.

96. The method according to claim 95, wherein the peptide modulator is an activator of gene expression.

97. The method according to claim 95, wherein the peptide modulator is an inhibitor of gene expression.

98. The method according to claim 88, wherein the modulation is mediated by a small molecule modulator of gene expression.

99. The method according to claim 98, wherein the small molecule modulator is an activator of gene expression.

100. The method according to claim 98, wherein the small molecule modulator is an inhibitor of gene expression.

101. The method according to any of claims 88-100, further comprising the step of purifying the secondary metabolite from a culture of the fungus.

See also

102. A genetically modified fungus, wherein the genetically modified fungus has an ability to produce secondary metabolites and the ability of the genetically modified fungus to produce secondary metabolites has been improved by any of the methods of claims 1-101.

103. A method for making a secondary metabolite, the method comprising culturing a genetically modified fungus according to claim 102 under conditions suitable for the production of secondary metabolites.

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